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(71) Applicant *(for all designated States except US)*: **ASTRAZENECA UK LIMITED** [GB/GB]; 15 Stanhope Gate, London W1Y 6LN (GB).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: **INCE, Francis** [GB/GB]; Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **DIXON, John** [GB/GB]; Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **HOLT, Philip, Ronald** [GB/GB]; Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB).

(74) Agent: **BAKHRU, Anna**; Astrazeneca, Global Intellectual Property, Mereside, Alderley Park, P.O. Box 272, Macclesfield,, Cheshire SK10 4GR (GB).

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(54) Title: PHARMACEUTICAL COMPOSITIONS

(57) Abstract: The present invention provides a pharmaceutical composition, pharmaceutical product or kit comprising a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, and a second active ingredient (B) being an anticholinergic muscarinic antagonist, for use in the treatment of obstructive airways diseases.

PHARMACEUTICAL COMPOSITIONS

The present invention relates to combinations of pharmaceutically active substances for use in the treatment of obstructive airways diseases.

In accordance with the present invention, there is therefore provided a pharmaceutical composition comprising, in admixture, a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, and a second active ingredient (B) being an anticholinergic muscarinic antagonist.

The invention also provides a pharmaceutical product comprising, in combination, a preparation of a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]-propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, and a preparation of a second active ingredient (B) being an anticholinergic muscarinic antagonist for sequential or separate use in therapy.

In another aspect, the invention provides a kit comprising a preparation of a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]-ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, a preparation of a second active ingredient (B) being an anticholinergic muscarinic antagonist, and instructions for the sequential or separate administration of the preparations to a patient in need thereof.

The combination of active ingredients according to the invention is advantageous because it is beneficial in the treatment of obstructive airways diseases including chronic obstructive pulmonary disease (COPD); and asthma, such as bronchial, allergic, intrinsic, extrinsic and dust asthma, particularly chronic or inveterate asthma (e.g. late asthma and airways hyper-responsiveness).

4-Hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one and pharmaceutically acceptable salts thereof are described in WO 93/24473. The active ingredient (A) is most preferably 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one hydrochloride.

Examples of the active ingredient (B) having anticholinergic activity include the muscarinic antagonists:

(*endo*, *syn*)-(±)-3-(3-Hydroxy-1-oxo-2-phenylpropoxy)-8-methyl-8-(1-methylethyl)-8-azoniabicyclo[3.2.1]octane bromide (ipratropium bromide);

(1α, 2β, 4β, 5α, 7β)-7-[(Hydroxydi-2-thienylacetyl)oxy]-9,9-dimethyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide (tiotropium bromide);

[7(S)-(1α, 2β, 4β, 5α, 7β)]-9-Ethyl-7-(3-hydroxy-1-oxo-2-phenylpropoxy)-9-methyl-3-oxa-9-azoniatricyclo[3.3.1.$0^{2,4}$]nonane bromide (oxitropium bromide); and

[3R-[3R*[S*(R*)]]]-α-(hydroxymethyl)-α-[2-(methylsulfinyl)ethyl]-benzeneacetic acid, 1-azabicyclo[2.2.2]oct-3-yl ester (revatropate).

Methods of assaying for muscarinic receptor activity are described, for example, by N. Watson et al in *Eur. J. Pharmacol.*, 285(2), 135-142 (1995).

The pharmaceutical composition of the invention may be prepared by mixing the first active ingredient (A) with the second active ingredient (B). Therefore, in another aspect of the present invention, there is provided a process for the preparation of a pharmaceutical composition which comprises mixing a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, with a second active ingredient (B) being an anticholinergic muscarinic antagonist. The pharmaceutical composition of the invention will typically comprise a total amount of first active ingredient (A) and second active ingredient (B) in the range from 0.05 to 99 %w (per cent by weight), more preferably in the

range from 0.10 to 70 %w, and even more preferably in the range from 0.10 to 50 %w, all percentages by weight being based on total composition.

The first and second active ingredients (A) and (B) may alternatively be administered sequentially or separately in any suitable order to treat obstructive airways diseases. By sequential is meant that the first and second active ingredients are administered one immediately after the other. They still have the desired effect if they are administered separately but less than about 4 hours apart, preferably less than about 2 hours apart, more preferably less than about 30 minutes apart.

The active ingredients may, and indeed usually will, be used in admixture with one or more pharmaceutically acceptable ingredients which may be selected, for example, from adjuvants, carriers, binders, lubricants, diluents, stabilising agents, buffering agents, emulsifying agents, viscosity-regulating agents, surfactants, preservatives, flavourings and colorants.

For the above-mentioned therapeutic uses the dosages administered will, of course, vary with the first and second active ingredients (A) and (B) employed, the mode of administration, the treatment desired and the disorder indicated. If the active ingredients are administered by inhalation, then the total daily dosage of first active ingredient (A) and second active ingredient (B) together is preferably in the range from 5 to 1500 μg, e.g. from 10 to 1450 μg or from 20 to 1400 μg.

The pharmaceutical composition, pharmaceutical product or kit according to the invention may be administered as divided doses from 1 to 4 times a day, and preferably once or twice a day.

The first and second active ingredients (A) and (B) may be administered topically (to the lung and/or airways) in the form of solutions, suspensions, aerosols and dry powder formulations; or systemically, e.g. by oral administration in the form of tablets, capsules,

syrups, powders or granules, or by parenteral administration in the form of solutions or suspensions.

For example metered dose inhaler devices may be used to administer the active ingredient(s), dispersed in a suitable propellant and with or without additional excipients such as ethanol, surfactants, lubricants or stabilising agents.

Suitable propellants include hydrocarbon, chlorofluorocarbon and hydrofluoroalkane (e.g. heptafluoroalkane) propellants, or mixtures of any such propellants. Especially preferred propellants are HFA-134a and HFA-227, each of which may be used alone or in combination with other propellants and/or surfactants and/or other excipients.

Nebulised aqueous suspensions or, preferably, solutions may also be employed, with or without a suitable pH and/or tonicity adjustment, either as a unit-dose or multi-dose formulations.

Dry powder inhalers may be used to administer the active ingredient(s), alone or in combination with a pharmaceutically-acceptable carrier, in the latter case either as a finely divided powder or as an ordered mixture. The dry powder inhaler may be single dose or multi-dose and may utilise a dry powder or a powder-containing capsule.

Metered dose inhaler, nebuliser and dry powder inhaler devices are well known and a variety of such devices are available.

Tablets and gelatin capsules, which may be coated if desired, containing the active ingredient(s) may, for example, also include one or more diluents, carriers, binders, lubricants or stabilising agents.

Injectable solutions of the active ingredient(s) may also contain, for example, one or more preservatives, stabilising agents, viscosity-regulating agents, emulsifying agents or buffering agents.

The present invention further provides the use of a pharmaceutical composition, pharmaceutical product or kit according to the invention in the manufacture of a medicament for the treatment of an obstructive airways disease.

Also, the present invention provides a method of treating, or reducing the risk of, an obstructive airways disease in a patient suffering from, or at risk of, the disease, which comprises administering to the patient a therapeutically effective amount of a pharmaceutical composition of the invention.

Still further, the present invention provides a method of treating, or reducing the risk of, an obstructive airways disease which comprises sequentially or separately administering (in any suitable order) to a patient suffering from, or at risk of, the disease

(a) a (therapeutically effective) dose of a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof; and

(b) a (therapeutically effective) dose of a second active ingredient (B) being an anticholinergic muscarinic antagonist.

CLAIMS

1. A pharmaceutical composition comprising, in admixture, a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, and a second active ingredient (B) being an anticholinergic muscarinic antagonist.

2. A composition according to claim 1, wherein, as first active ingredient (A), 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one hydrochloride is used.

3. A composition according to claim 1 or claim 2, wherein, as second active ingredient (B), ipratropium bromide, tiotropium bromide, oxitropium bromide or revatropate is used.

4. A process for the preparation of a pharmaceutical composition as defined in claim 1 which comprises mixing a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, with a second active ingredient (B) being an anticholinergic muscarinic antagonist.

5. Use of a pharmaceutical composition as claimed in any one of claims 1 to 3 in the manufacture of a medicament for the treatment of an obstructive airways disease.

6. Use according to claim 5 wherein the obstructive airways disease is chronic obstructive pulmonary disease or asthma.

7. A method of treating, or reducing the risk of, an obstructive airways disease in a patient suffering from, or at risk of, the disease, which comprises administering to the

patient a therapeutically effective amount of a pharmaceutical composition as defined in any one of claims 1 to 3.

8. A method according to claim 7, wherein the obstructive airways disease is chronic obstructive pulmonary disease or asthma.

9. A pharmaceutical product comprising, in combination, a preparation of a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]-ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, and a preparation of a second active ingredient (B) being an anticholinergic muscarinic antagonist for sequential or separate use in therapy.

10. A product according to claim 9, wherein, as first active ingredient (A), 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one hydrochloride is used.

11. A product according to claim 9 or claim 10, wherein, as second active ingredient (B), ipratropium bromide, tiotropium bromide, oxitropium bromide or revatropate is used.

12. Use of a product as claimed in any one of claims 9 to 11 in the manufacture of a medicament for the treatment of an obstructive airways disease.

13. Use according to claim 12 wherein the obstructive airways disease is chronic obstructive pulmonary disease or asthma.

14. A kit comprising a preparation of a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof, a preparation of a second active ingredient (B) being an anticholinergic muscarinic antagonist, and instructions for the sequential or separate administration of the preparations to a patient in need thereof.

15. A kit according to claim 14, wherein, as first active ingredient (A), 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one hydrochloride is used.

16. A kit according to claim 14 or claim 15, wherein, as second active ingredient (B), ipratropium bromide, tiotropium bromide, oxitropium bromide or revatropate is used.

17. A method of treating, or reducing the risk of, an obstructive airways disease which comprises sequentially or separately administering to a patient suffering from, or at risk of, the disease

(a) a dose of a first active ingredient (A) being 4-hydroxy-7-[2-[2-[3-[2-phenylethoxy]-propylsulphonyl]ethylamino]ethyl]-1,3-benzothiazol-2(3*H*)-one or a pharmaceutically acceptable salt thereof; and

(b) a dose of a second active ingredient (B) being an anticholinergic muscarinic antagonist.